

US EPA ARCHIVE DOCUMENT

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

EPA/630/R-06/001
External Review Draft
February 2006

Harmonization in Interspecies Extrapolation: Use of $BW^{3/4}$ as Default Method in Derivation of the Oral RfD

Risk Assessment Forum Technical Panel

Authors:

Gary L. Foureman, Office of Research and Development
Elaina M. Kenyon, Office of Research and Development

Risk Assessment Forum Technical Panel:

Vicki L. Dellarco, Office of Pesticide Programs, Co-Chair
Deirdre L. Murphy, Office of Air and Radiation, Co-Chair
Brenda P. Foos, Office of Children's Health Protection
Gary L. Foureman, Office of Research and Development
Elaina M. Kenyon, Office of Research and Development
Gregory G. Miller, Office of Policy, Economics, and Innovation

Contributors:

Hugh A. Barton, Office of Research and Development
Annie M. Jarabek, Office of Research and Development

Risk Assessment Forum Staff:

Resha M. Putzrath, Health Science Coordinator
William P. Wood, Executive Director

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

Table of Contents

- Executive Summary
- I. Background
- II. Toxicologically equivalent doses in the inhalation RfC and the oral RfD.
- III. BW scaling for deriving toxicologically equivalent doses in the oral RfD
- IV. Considerations in Using $BW^{3/4}$ Scaling as a Default for estimating Toxicologically Equivalent Doses
- V. Conclusions
- VI. References

Appendices

- A. $BW^{3/4}$ scaling vs $BW^{1/1}$ – a comparison
- B. The Interspecies $BW^{3/4}$ Oral Dosimetric Adjustment Factor (DAF) $BW_h^{-1/4} / BW_a^{-1/4}$
- C. The Oral DAF and Portal-of-entry Considerations
- D. Hierarchy of approaches for interspecies extrapolation for inhalation dosimetry (from USEPA 1994)

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

Executive Summary

The Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animals, with the preferred approach being physiologically based toxicokinetic modeling. Intermediate approaches would include using some chemical-specific information. In lieu of data to support either of these approaches, body weight scaling to the $3/4$ power, i.e., $BW^{3/4}$, is endorsed as a general default procedure to extrapolate toxicologically equivalent doses of chronic orally administered agents from laboratory animals to humans for the purposes of deriving an oral Reference Dose, RfD. Use of $BW^{3/4}$ in derivation of RfD values is parallel with its current Agency use in derivation of cancer oral slope factors. Thus, this default scaling procedure is a point of harmonization between the two main Agency oral dose-response procedures.

The scope of this document is limited to recommending a generic default procedure that is viewed as an informed species-specific dosimetric adjustment factor (DAF) that addresses predominately toxicokinetic and some toxicodynamic aspects of the interspecies uncertainty factor, UF_A . Use of this procedure would result in derivation of a human equivalent exposure, specifically a human equivalent dose, HED, that is to be used in derivation of the oral RfD in a manner parallel to the human equivalent concentration, the HEC, in derivation of an inhalation RfC.

It is recognized that this procedure, as all default procedures, may not always predict oral exposures associated with precisely toxicologically equivalent doses for specific chemicals. It should be emphasized that other factors not discussed in this document can also have a significant effect on interspecies adjustments. As a general default procedure, however, it may be anticipated to provide reasonable descriptions of average behavior of many chemicals much of the time. As with the HEC, chemical-specific values as indicated by available data and information would supersede or modify this default procedure for the HED, with the optimal procedure being use of a physiologically-based toxicokinetic model.

This document should be used in combination with other risk assessment tools, guidance, and guidelines. U.S. Environmental Protection Agency (EPA or the Agency) risk assessments may be conducted differently than envisioned in this guidance for many reasons including, for example, new information, new scientific understanding, or different science policy judgment. The practice of assessing interspecies differences from exposure to toxicants continues to develop, and specific components of this guidance may become outdated or may otherwise require modification in individual settings. It is EPA's intent to use, to the extent practicable and consistent with Agency statutes and regulations, the best available science in its risk assessments and regulatory actions, and this guidance is not intended to provide any substantive or procedural obstacle in achieving that goal. Therefore, this guidance has no binding effect on EPA or on any regulated entity. Where EPA does use this guidance in developing exposure and risk

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

assessments, it will be because EPA has decided in the context of that assessment that the approaches from this guidance are suitable and appropriate. This judgment will be tested through peer review, and the risk assessment will be modified to use different approaches if appropriate.

This guidance does not establish any substantive “rules” under the Administrative Procedure Act or any other law and has no binding effect on EPA or any regulated entity, but instead represents a non-binding statement of policy.

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

I. Background

This science policy paper is in response to the Agency's Risk Assessment Forum's effort to development and promote harmonized approaches for all toxicity endpoints used in human health risk assessment. Towards the goal of harmonization, the specific purpose of this science policy paper is to recommend procedures, inclusive of default procedures, that will be used to estimate oral exposures in terms of human equivalents for all toxicologic endpoints. In doing so this work is intended to follow and be concordant with the mode-of-action as the guiding paradigm for toxicologic evaluations, both cancer and noncancer (USEPA 2005; USEPA 1994; USEPA 2002). That the dose at the target site, the internal dose, "is the ultimate determinant of risk" (NRC, 1994), is a fundamental generalization of this paradigm.

Considerations in application of procedures identified in this paper, such as different exposure conditions, toxicokinetics, and different life-stages for all toxicological endpoints, will also be addressed to the extent allowed by the current information.

Human risk assessments are often based on toxicity data from laboratory animal species thereby necessitating a number of extrapolations for estimating the exposure conditions for which a similar toxicity is projected. A critical step is relating the exposure-dose-response relationships for laboratory animals to those pertaining to humans. That is, the need to adjust the exposure used in an animal study to a human "equivalent" exposure. The most scientifically sound approach by which this may be accomplished is through the use of chemical- and species-specific toxicokinetic and toxicodynamic information to estimate the internal dose at the target tissue. Note that this approach is based on and concordant with the mode-of-action paradigm discussed above. In most cases, however, there are insufficient toxicokinetic/dynamic data available to compare internal dose between different species. In these cases, science-based intermediate and default approaches are needed to derive the estimate of human equivalent dose or concentration.

The methods used by the Agency to extrapolate from animal experimental exposures/doses to human equivalent estimates have evolved since the assessments of the early 1980s. And there have been differences in that evolution for oral vs inhalation exposures, as well as for cancer vs non-cancer assessment approaches. The Agency's cancer risk guidelines have and continue to endorse the application of scaling procedures, either on surface area or on body weight, for purposes of default interspecies extrapolation in calculation of a Human Equivalent Exposure, HEE. This document recognizes and uses the term HEE in referring collectively to human exposures¹ via any route. When exposures are via the oral route, the more specific term Human Equivalent

¹ The term "exposure", as used here, is roughly analogous here to the terms "administered" or "potential dose" as used in the *Guidelines for Exposure Assessment* (USEPA 1992).

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

Dose, HED, may be applied; when via the inhalation route the term Human Equivalent Concentration, HEC, may be applied.

In EPA cancer assessments for the oral route prior to 1992, laboratory animal exposures being used to extrapolate to a human cancer risk estimate were typically adjusted based on surface area scaling (derived using $BW^{2/3}$ as (Anderson et al., 1983; USEPA 1992, 1986). In cancer assessments for the inhalation route prior to development of the Agency's inhalation dosimetry methodology (USEPA 1989; 1994), interspecies extrapolation from the animal exposure concentration differed depending on judgment regarding the chemical's absorption following inhalation. For chemicals judged to be completely absorbed upon inhalation, surface area scaling ($BW^{2/3}$) was employed in the extrapolation, e.g., dichloromethane (USEPA 1985).²

The interspecies extrapolation practice for cancer assessments was recommended in 1992³ when the U. S. EPA in collaboration with the Food and Drug Administration and the Consumer Product Safety Commission proposed the use of a cross-species scaling factor for administered dose based on equivalence of body weight (in mg/kg) to the $3/4$ power per day ($BW^{3/4}/\text{day}$) (USEPA 1992). While acknowledging that empirical data on comparative carcinogen potency was compatible with scaling either by body weight or surface area ($BW^{2/3}/\text{day}$), the document proposed use of $BW^{3/4}$ because of its underlying basis on established allometric interspecies variation in anatomy and physiology, much of which is explored and documented further in this policy paper and accompanying appendices. Similarly, the Agency's 2005 cancer risk guidelines (USEPA 2005) endorse the application of $BW^{3/4}$ for purposes of interspecies extrapolation when chemical-specific data are absent.

The U.S. EPA 1992 action (USEPA 1992) provided a source of standardization for predictive cancer risk assessment via the oral route. However, the procedures employed for derivation of the Reference Dose (RfD), the Agency's traditional dose-response method for noncancer effects from a toxic agent via the oral route, were and remained quantitatively different. In the derivation of an RfD, the dose administered orally is expressed in mg/kg-day and is directly proportional across species on a body weight basis, i.e., BW^1 vs $BW^{3/4}$. An uncertainty factor, UF_A , is subsequently applied to the laboratory animal exposure for consideration for interspecies extrapolation.

Since 1989, extrapolation from laboratory animal inhalation exposure concentrations to HECs has been performed as per *Interim Methods for Development of Inhalation Reference Doses* (USEPA 1989) and *Methods for Derivation of Inhalation Concentrations and Application of Inhalation Dosimetry* (USEPA 1994), hereafter *Methods*. *Methods* gives preference to the use of toxicokinetic modeling for

² Subsequent toxicokinetic analysis with dichloromethane (USEPA 1987, 1989) informed the *Methods* development leading to different default adjustments for remote acting gases.

³ The Agency has since reaffirmed the method in carcinogen risk assessment (see USEPA 1999, 2001).

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

extrapolation, but also recognizes the use of intermediate and default options for exposure concentration adjustment approaches based on consideration of physicochemical characteristics of a given agent as key determinants of interaction with the respiratory tract and ultimate disposition of the agent in the body. In these procedures, which may be considered as inhalation dosimetry, particles and gases are treated separately, and the type of toxicity observed, respiratory tract (i.e., portal-of-entry) or toxicity remote to the portal-of-entry tissues, determines the adjustment procedure applied. Since its inception, derivation of the HEC for this extrapolation has been utilized in cancer and noncancer inhalation assessment procedures. With regard to the latter, the RfC (initially termed an “inhalation Reference Dose” or RFD_i) originated with the development of *Methods*. Concordant with the RfD process, *Methods* includes recognition of an uncertainty factor for uncertainties associated with interspecies extrapolation, UF_A, with the default value of this UF automatically reduced (e.g., by half, logarithmically) in recognition of the dosimetric adjustment employed to estimate the human equivalent concentration inherent in the derivation of the HEC.

II. Toxicologically Equivalent Doses in the inhalation RfC and oral RfD

Estimating toxicologically equivalent doses - Extrapolation and Dosimetry in the Inhalation RfC

As discussed above, dose-response assessment for human health, by the Agency as well as the entire risk assessment community, often uses health effect information from laboratory animals, requiring extrapolation to humans. The goal of the extrapolation procedure is to determine toxicologically equivalent doses between the animals and humans, ideally by “matching” with respect to the internal dose, or, in other words, determining the externally applied exposure for humans that would result in the same internal dose as determined from the animal toxicity information. In derivation of the RfC,⁴ this extrapolation is accomplished for an inhaled agent through application of a suite of procedures that range from application of a sophisticated physiologically-based toxicokinetic (PBTK) model to default procedures for site-specific dosimetry.

These default procedures are described fully in the Agency’s 1994 *Methods* and are represented here schematically in Figure 1a⁵. Dosimetric adjustment factors (DAF) are used to extrapolate laboratory animal exposure concentrations to human equivalent exposure concentrations. The DAFs differ with chemical categories and include the Regional Gas Dose Ratio (RGDR) for gases and the Regional Deposited Dose Ratio (RDDR) for particles. When the default approaches are employed, the interspecies

⁴ The same suite of procedures is applied in determining the HEC when deriving the inhalation cancer risk estimate.

⁵ It is noted that this description of the default approach is, for the purposes here, a simplification of the recommended process which is based on the selection of the measure of dose which best expresses the internal dose at the target. Consideration of duration adjustment, i.e., from discontinuous to continuous exposures, is not described here. See USEPA (1994) for the full recommended methodology.

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

uncertainty factor is reduced. While the remaining uncertainty may include elements of toxicokinetics as well as toxicodynamics, the dosimetric adjustment, for simplicity is generally described as addressing variability in chemical disposition or toxicokinetics. A more in-depth discussion of the aspects of inter- and intra-species extrapolation considered to be accounted for with the default dosimetric adjustments is presented elsewhere (Jarabek 1995; Bogdanffy and Jarabek, 1995a; USEPA 1994).

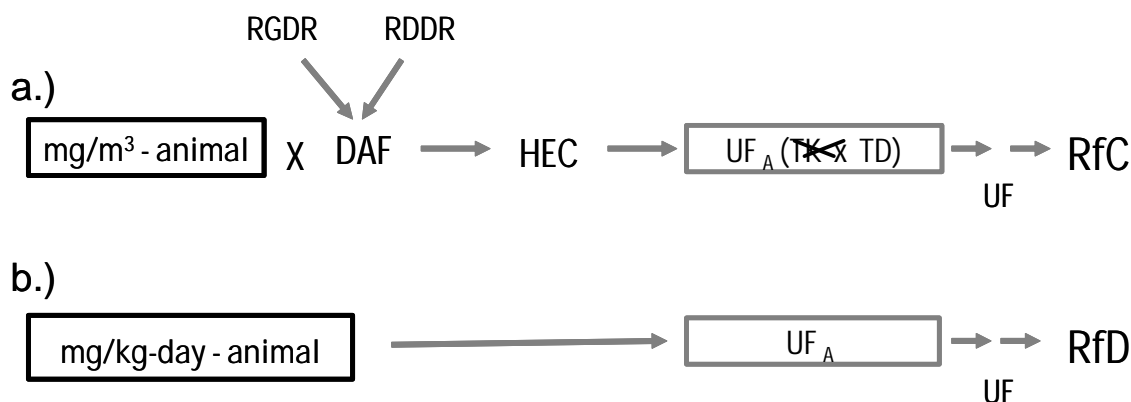


Figure 1. Schematic of current procedures in the RfC (a.) and RfD (b.) processes. A “human equivalent” concentration or HEC (or another HEE) is derived in the case of the RfC but not the RfD. UF_A denotes the animal-to-human uncertainty factor with UF representing other factors applied for various extrapolations (as per *Methods*). In the RfC pathway, TK denotes toxicokinetic and TD toxicodynamic components of the UF_A .

Figure 1 shows the experimental animal exposure of an agent⁶, in ppm or mg/m^3 , extrapolated to a Human Equivalent concentration, an HEC, via application of “Dosimetric Adjustment Factors” or DAFs. DAFs are based on the determinants of disposition considered most influential to differences between animals and humans. For example, with inhaled agents that affect the upper airways, DAFs are constructed from the surface areas of various regions of the airways and the minute inhalation volume of the species involved. For inhaled agents that involve transport by blood to affect systemic tissues, DAFs are constructed from partition coefficients of the agent (e.g., blood:gas and blood:tissue). The DAFs listed above are actually ratios constructed of animal and human values for these default determinants of disposition. As application of this ratio is projected to result in the human exposure that would bring about the same internal dose as the laboratory animal exposure to which it is applied, the DAF may also be considered as a factor used to “normalize” an animal external exposure to the

⁶ In this case, the animal exposure extrapolated is a point of departure (e.g., NOAEL, LOAEL or BMDL) derived from analysis of the findings from an animal study.

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

corresponding human external exposure under the guiding paradigm that a common internal dose is the ultimate determinant of risk (*see* Appendix D).

In the current RfC process, the default application of DAFs is considered to produce human equivalent concentrations associated with toxicokinetically equivalent doses to the human tissue. Application of the default DAFs is not generally described as accounting for the toxicodynamic portion of response as is indicated in Figure 1a, although as described above, that is a simplification. Other chemical specific information may inform consideration of toxicodynamic differences. As a simplification, Figure 1a shows the elimination of the TK component from the UF_A in consideration of the use of an HEC and implies the residual is within the toxicodynamic (TD) component although depending on the chemical assessment this may or may not be the case.

Extrapolation in the Oral RfD Derivation Process

Currently, no document or dosimetry procedures comparable to the *Methods* exist for the oral RfD. As with the RfC, derivation of this reference value is frequently reliant on experimental animal data. In general, the UF_A is applied along with other UFs to the animal experimental dose to give the oral RfD value. Figure 1b reflects this simplified process showing application of the UF_A with no “HED” formally calculated. Appendix A illustrates the numerical consequences of this practice (e.g., use of $BW^{1/1}$ vs $BW^{3/4}$).

III. $BW^{3/4}$ Scaling for Deriving Toxicologically Equivalent Doses in the Oral RfD

Scaling in Cross-Species Extrapolation

Use of a fractional power of body weight, most often $BW^{3/4}$, as a means to derive toxicologically equivalent doses across species has become widely accepted in the risk assessment community (e.g., USEPA 1986, 1992, 2005). The basis for this acceptance is along several lines. An extensive and historical literature exists on general allometric relationships between $BW^{3/4}$ and physiological and biochemical processes, mostly related to kinetics (Kleiber 1932, 1961). There exists also considerable empirical information on the kinetics and toxicology of pharmacologic agents that have been examined in relation to BW (e.g., Dedrick et al. 1970, 1973). Much of the information related to these arguments are described and explained in the recent report of Rhomberg and Lewandowski (2004) and in the 1992 U.S. EPA Federal Register notice (USEPA 1992). Some of the more compelling information on BW scaling in relation to basic life processes and to the effects and kinetics of pharmaceuticals and toxic agents follows.

Interspecies $BW^{3/4}$ Scaling & Life Processes

Kleiber’s synthesis of data on energy utilization in mammals resulted in his published observations and recommendations that the allometric relationship of $BW^{3/4}$ is an accurate reflection of “metabolic body size” in mammals (Kleiber 1947). Subsequent to

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

his work, a large number of characteristics and functions of mammalian biological systems were examined for their relationship with BW. Table 1 shows some examples. Volumes and capacities tend to retain their proportionality across species, i.e., $BW^{1/1}$. A great number of physiological processes in addition to those listed here are proportional to $BW^{3/4}$ (West et al. 1997, Enquist et al. 1998).

Function	Units	Species Scaling
Energy Utilization	(kcal/day)	$BW^{3/4}$
Glomerular filtration	(L/min)	$BW^{3/4}$
Glucose turnover	(mg/min)	$BW^{3/4}$
Heart rate	(min^{-1})	$BW^{-1/4}$
Respiratory rate	(min^{-1})	$BW^{-0.26}$
Blood volume	(L)	$BW^{1/1}$
Vital capacity	(mL)	$BW^{1/1}$
Food consumption	g/day	$BW^{3/4}$
Water consumption	L/day	$BW^{3/4}$

Table 1. Cross-species body weight scaling for various metabolic and physiological functions.

From these relationships it can be deduced in mice and humans, for example, that weight increases in direct proportion with blood volumes and organ weights. Other processes, e.g., those involving flow and energy production and food and water consumption, do increase in absolute values but in proportion to only the three-quarter power of the body weight. It may also be seen that in processes involving rates and time, a decrease in the absolute value may actually occur. Thus although the body mass and absolute heart mass in humans are both about 2300-fold greater in humans than in mice (scaling to $BW^{1/1}$), cardiac output in humans is only about 300-fold greater than in mice (scaling to $BW^{3/4}$) whereas the heart rate in humans is about 7-fold less than in mice (scaling to $BW^{-1/4}$). The latter relationship where certain processes between species are related one to another in an inverse manner (i.e., are actually decreased rather than increased) follows from $BW^{3/4}$ allometry by rates where processes varying by a three quarter power are normalized against an aspect that varies directly, i.e, BW^1 such that

$$BW^{3/4} / BW^1 = BW^{-1/4}.$$

This inverse relationship between the absolute rates of processes such as glomerular filtration, minute ventilatory volume and cardiac output and BW is supported by considerable empirical information and has been crystallized in the concept of physiological time across species (e.g., USEPA, 1992). Thus processes that are related by BW to a quarter power, such as physiological time, are actually corollaries of $BW^{3/4}$ scaling that have been predicted mathematically and substantiated by empirical

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

observations. This concordance between hypothesis and observations imparts considerable credence to the overall relational theory of $BW^{3/4}$ scaling.

Interspecies $BW^{3/4}$ Scaling & Toxicity Processes

The $BW^{3/4}$ allometric scaling relationship of Kleiber (1932, 1961) was established with general kinetic processes of living systems. The relevancy of these general processes to the more refined relationship of kinetics of pharmaceuticals and other xenobiotics, such as toxicants, has also been examined. In general, the information available in this area supports the three quarter power relationship (including the quarter power relationship) for toxicologic and toxicokinetic behavior of a number of compounds over a reasonable number and range of species.

Travis and White (1988) undertook an extensive analysis of the maximum tolerated dose of the dose-response relationship of 27 direct acting agents (i.e., where the agent causing toxicity is the administered or parent chemical) administered orally (once per day, 5 days a week) in mice, rats, dogs, monkeys, hamsters, and humans. They then used regression techniques to determine the optimal power of body weight to achieve the best fitting relationship. They reported $BW^{0.73}$ (95% confidence bounds $BW^{0.69-0.77}$) as the geometric mean of the cross-species predictions. This study, which is actually a reanalysis of data sets from two other studies (Freireich et al., 1966 and Schein et al., 1970) thus gives support to the relationship of $BW^{3/4}$ in making interspecies extrapolations for direct acting toxicologic agents. The analysis also rejected the relationships of $BW^{1/1}$ (the exponent associated with direct proportionality) and $BW^{2/3}$ (the exponent associated with body surface area scaling) although a subsequent report offered an analysis suggesting that $BW^{2/3}$ still may fall within the confidence bounds (Watanabe et al., 1992).

The analyses by Boxenbaum (1982) and Dedrick (1970) of elimination rate constants for 8 drugs in 4 different species found this parameter to be proportional to $BW^{0.22}$ which is reasonably close to the expected value for $BW^{1/4}$ scaling related to time processes of $BW^{3/4}$.

Recently, Kirman et al (2003) employed PBTK models as tools to assess the performance of allometric scaling. These authors employed PBTK models of 12 different volatile and lipophilic compounds to estimate the kinetic disposition of these various agents in yielding a measure of internal dose (area under the curve or AUC) in mouse, rats and humans. Model estimates were obtained under continuous and gavage exposure conditions over a range of experimental exposures considered low (0.0001-1 mg/kg-day) and high (10-10,000 mg/kg-day). The estimates from the models were then compared to predictions calculated from allometric scaling of the administered dose based solely on $BW^{3/4}$. The results indicated that $BW^{3/4}$ generally performed better at relatively low administered doses (where metabolism is not saturated and clearance rates were pseudo-first order) than at high administered doses. The results also indicated that the scaling factors were applicable in oral administration not only to parent chemical but

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

also for the formation of stable metabolites and amount metabolized (first-order pathways) (see *Metabolism and Clearance* below).

IV. Considerations on Using $BW^{3/4}$ Scaling as a Default for estimating Toxicological Equivalent Doses

Metabolism and Clearance

Observations of a fractional power relationship between body weights with regard to processes across species has been hypothesized to be related fundamentally to differences in exchange surfaces and distribution networks, that constrain internal concentrations and flux associated with general metabolic processes of endogenous substances and reactants for all living systems (West et al., 1997; Enquist et al., 1998).

The applicability of this general body weight scaling relationship to more specific metabolic processes, such as xenobiotic metabolizing systems involved in the clearance or activation of exogenous substances (where disproportional relationships among species often exist) would depend on the similarity in the kinetic behavior of the exogenous substance to endogenous reactants. The degree of similarity or dissimilarity would reflect whether the parent or a stable or reactive metabolite is the relevant dose to the target tissue (USEPA, 1992; O'Flaherty, 1989; Beck and Clewell, 2001) and on the specific kinetics of the clearance process as to whether they are first order or capacity-limited (O'Flaherty, 1989). Both of these factors prominently influence the dose to the target tissue over time, i.e., the AUC (see below).

Accordingly, $BW^{3/4}$ scaling would apply most appropriately to those exogenous substances for which the unmetabolized parent or a stable metabolite is the relevant toxic species and clearance is according to first-order processes (USEPA, 1992). Conversely, the applicability of $BW^{3/4}$ scaling when toxicity is a consequence of exposure to a very reactive metabolite (or parent compound) that is not removed from the site of formation, such as toxic effects occurring at the portal of entry, is less well supported (Beck and Clewell, 2001; Travis, 1990).

Measure of Delivered Dose: choice of the appropriate dose metric

As pointed out above, the species BW scaling interrelationships among volumes ($BW^{1/1}$), physiological processes ($BW^{3/4}$), and rates ($BW^{-1/4}$) have been shown to result in a normalization of dose across species (USEPA, 1992) with respect to time. This normalization, based on the concept of physiological time implicit in $BW^{-1/4}$ scaling, is in terms of exposure to a concentration over some duration of time, i.e., area under the curve (AUC) that is adjusted for species. Thus the measure of dose that is being scaled for kinetic equivalency between species in this process is the AUC (O'Flaherty, 1989).

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

It is recognized that toxicants may not exert their effects through a single mode or mechanism and that in some cases, measures of delivered dose other than AUC may be more appropriate. However, for agents causing cumulative irreversible damage, a common definition of toxicity, an expression of integrated exposure such as AUC may be considered appropriate (recognizing the caution raised in the previous section regarding toxicity at the portal of entry).

Early Life-Stages

Historically, investigations with BW scaling have dealt almost exclusively with adult organisms. Moreover, experimental toxicity information is typically generated through exposure of adult (i.e., fully developed) organisms. Thus, the typical default application of $BW^{3/4}$ scaling has been for cancer assessment (USEPA 2005) and would be in the derivation of the RfD (as considered here) to scale the administered exposure for the laboratory animal to that for the adult human. As the individual to which the toxicant is administered is generally an adult animal, this practice would be generally employed even when the “target tissue” is a fetus or developing pup such as in developmental or multigenerational reproductive studies.

Although the context for this document largely is traditional Agency methods such as the chronic reference dose, in some situations, where the focus is specifically on children, the Agency may have animal exposure data particular to young animals and may be interested in derivation of an exposure value particular to a non-adult human subpopulation rather than such a value pertinent to the larger population. In those instances, scaling from the young animal exposure to a young human exposure may be desirable. The following discussion is intended to be informative to such situations, as well as to application of the traditional methods.

Arguments have been made that varying and disproportionate growth rates among species during and around puberty would not be well characterized by $BW^{3/4}$ scaling (USEPA, 1992; Rhomberg and Lewandowski, 2004). Recently available analyses of pharmacokinetic data on therapeutic drugs for different age-groups of children, however, indicate that a number of toxicokinetic parameters, including activity of various xenobiotic metabolizing enzymes, essentially reflect adult values by 6 months of age with the largest differences from the adult values occurring in the first 2 months (Ginsberg et al. 2002, 2004). The implication of these differences at around 2 months is that $BW^{3/4}$ scaling may not adequately characterize these PK differences (i.e., those observed within the first 2 months). Hattis analyzed clearance rates on a $BW^{1/1}$ basis for a number of different drugs over a wide-ranging spectrum of clearance mechanisms in adults and children/infants (Hattis et al. 2004). These data showed that from the age range of 2 months to 12 years, clearance rates were actually higher in children than in adults, whereas values for the very young (1-8 weeks, full-term neonates and premature neonates) were deficient relative to adults, ratios for premature infants being about $1/2$ those for adults. Reconstruction of these data using instead clearance rates on a $BW^{3/4}$

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

basis resulted in ratios that approximated 1 (children equal to adults) down to 6 months of age. This reconciliation of data indicates that the occurrences of higher clearance rates in children (down to about 6 months) relative to adults are explained by $BW^{3/4}$ allometry. The impact of this in consideration of interspecies scaling is illustrated in Table 2, although it is noted that this Agency paper is not recommending scaling from adult animal to other than adult human exposure.

Table 2. Comparison of $BW^{3/4}$ in extrapolating intake or administered dose from a rat to a 70 kg adult and to a 10 kg child.

Intake or Administered Dose (10 mg/kg)	Species	Scaling	BW(h)/ BW(a)	Body Weight Scaling Factor	Scaled Human Intake or Administered/Potential Dose (mg/kg)
2.5 mg/0.25 kg	Rat	$BW^{3/4}$	70 kg Adult $70 / 0.25 = 280$	$280^{3/4} = 68$	2.4 mg/kg (68 x 2.5) or 170 mg / 70 kg
2.5 mg/0.25 kg	Rat	$BW^{3/4}$	10 kg Child $10 / 0.25 = 40$	$40^{3/4} = 16$	4.0 mg/kg (16 x 2.5) or 40 mg / 10 kg

Clewell et al. (2004) used a PBTK lifestage model that integrated various age- and gender- specific differences, inclusive of an age category indicated as “birth to 6 months”. The authors examined measures of internal dose (e.g., parent, circulating or reactive metabolite) for 6 different chemicals, and reported that values for each were within a factor of 2 across the age groups evaluated, although larger transient variations were predicted particularly during the neonatal period. Their results indicated that the most important age-related PK factor appeared to be the potential for decreased clearance of a toxic chemical in the perinatal period although this same factor could also result in reduced production of a reactive metabolite. One attempt to systematically evaluate quantitative scaling differences in toxicodynamic processes across lifestages (Hattis 2004) noted that data for such an analysis are limited. However, rapid growth rates in childhood and physiological changes associated with puberty suggest that this is an area of high uncertainty with respect to $BW^{3/4}$ scaling.

Differential development of xenobiotic metabolizing enzymes for the very young (≤ 2 months age) does not necessarily indicate greater sensitivity of the young to toxic agents. For example, less activity of an activating enzyme may mean less, not more, potential hazard from a compound requiring activation to be hazardous. Similarly, excess capacity in other pathways, such as with certain detoxifying or repair enzymes, may be sufficient to offset higher activities of activating enzymes. Thus, examining parameters individually is insufficient to draw conclusions regarding differences in internal dosimetry (e.g., Kedderis, 1997). Evaluation of these differences needs to be investigated at the basic level of dose at the target site, preferably by integrative methods such as PBTK models or other biologically-based modeling approaches (Ginsberg et al., 2002,

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

2004). This is because internal dose to target tissue is a balance between competing processes of metabolism, excretion, binding and other toxicokinetic processes.

It is noteworthy that the use of $BW^{3/4}$ scaling to derive a human equivalent dose for children yields a higher intake than does scaling to an adult human. This calculation and its result are shown for the sole purpose of demonstrating this point, in Table 2. It can be seen that use of $BW^{3/4}$ scaling would project that a 10 kg child would require a 1.6-fold (4.0 divided by 2.4) higher intake than a 70 kg adult to achieve a toxicologically equivalent dose. The data assembled and analyzed by Hattis et al. (2003a) give support to this observation in that, overall, the elimination rate constants for 44 different pharmaceuticals were somewhat lower in adults than those measured in children from ages 10 years down to about eight weeks. These differences indicate that $BW^{3/4}$ scaling – from adult animal to adult human – may generally and “conservatively” characterize interspecies extrapolation for humans of various ages, however with increased uncertainty for ages ≤ 8 weeks (Hattis et al., 2004).

As present, no systematic evaluation of the impact of $BW^{3/4}$ scaling on toxicodynamic processes across lifestages exists which makes this an area of uncertainty. It should be noted, however, that the RfD approach includes consideration of an UF for intraspecies variation in susceptibility due to the possibility that a given data base may not be representative of the exposure-response relationship for some susceptible subgroups within the overall population. As with the UF_A , this UF is also considered to comprise both toxicokinetic and toxicodynamic components (Renwick and Lazurus, 1998).

Toxicokinetics and Toxicodynamics in Toxicological Equivalence

Species differences in dose-response may be elicited both as a consequence of distribution of agent affecting the target-tissue dose between species and from intrinsic differences in the tissue response between species. Achieving “toxicological equivalence” across species requires that aspects of both toxicokinetics and toxicodynamics be considered. Therefore using $BW^{3/4}$ to achieve “toxicological equivalence” for interspecies differences implies that scaling is inclusive of both aspects.

From the preceding discussion on allometry, it is apparent that many physiological processes relating to kinetics do conform to a $BW^{3/4}$ relationship. This is not to say, however, that $BW^{3/4}$ scaling encompasses all kinetic processes related to toxicity. Neither does this statement intend to indicate that $BW^{3/4}$ scaling does not address any dynamic aspects of toxicity. It has been established, for example, that many processes considered to be toxicodynamic in nature, e.g., cellular repair and regeneration, signaling cascades and proliferative responses, scale also as a fractional power of BW (see Rhomberg, 2004 and USEPA, 1992 for additional examples).

It is necessary to acknowledge the overlap in kinetic and dynamic factors addressed by $BW^{3/4}$ scaling. That $BW^{3/4}$ scaling applies only to metabolic-type kinetic processes

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

between species is a misconception. Many potential modulating factors that may be considered as dynamic, such as the intrinsic sensitivity of the target site, may be highly species dependent. The concept to be conveyed is that cross species $BW^{3/4}$ scaling toxicologically equivalent doses predominately addresses factors involved in estimating toxicokinetics as well as some toxicodynamic factors. This concept is critical to how the interspecies uncertainty factor (UF_A) is applied in derivation of the RfD (see below).

Chronic vs Acute Scenarios in Application of $BW^{3/4}$ Scaling

The focus of this default procedure is for the RfD and oral cancer assessments, both of which are currently concerned with lifetime repeated exposure scenarios. Application of this procedure to scenarios of shorter durations such as, for example, acute, may warrant further consideration (some of which is discussed in Hattis 2003b).

As discussed above, $BW^{3/4}$ scaling is understood to address aspects of both TK and TD, the latter being inclusive of many repair-type processes. In the case of a single exposure eliciting frank toxicity (e.g., sudden, severe and overwhelming damage) accomplished by an immediate and intolerable level of damage to some critical biological pathway, repair processes (i.e., TD), however, $BW^{3/4}$ scaling would not generally be relevant. This case is in contrast to chronic exposures, e.g., repeated daily exposures over a lifetime, where the organism or tissue has time available for these repair processes to be elicited and functional, and to less severe acute exposures, in which the level of damage is not severe.

Rhomberg and Wolff (1998) examined patterns in the correspondence of LD_{50} values from a single oral administration across several species. They found that direct scaling by body weight (i.e., $BW^{1/1}$), rather than scaling to $BW^{3/4}$, best fit the data. One limitation of this analysis is that most of the data were obtained in species of similar size (i.e., mouse, rat, guinea pig, hamster) where the correlation was strongest. Rhomberg and Caprario (1999) extending the findings of Rhomberg and Wolff (1998) by examining information available on larger species via collating data from administration routes other than oral (i.e., intravenous, intraperitoneal and intramuscular). LD_{50} values of over 3,000 agents were evaluated in pair-wise species comparisons across 8 species (mouse, rat, hamster, guinea pig, rabbit, cat, dog and monkey). Results were similar to the oral LD_{50} analysis, indicating that for lethal acute exposures, scaling to $BW^{1/1}$ provided a good extrapolation factor across species.

Thus, due to these toxicodynamic considerations, $BW^{3/4}$ would most likely not be applicable to scenarios under a definition of an acute exposure focused on the occurrence of immediate and frank or lethal effects. Application of $BW^{3/4}$ is considered a reasonable approach, however, for acute exposures involving other, less severe, definitions of acute effects in which the operative physiological processes are comparable to those for the chronic scenario.

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

Portal-of-entry Issues for Oral Exposure

The utility and limitations of allometric scaling ($BW^{3/4}$) for oral route portal-of-entry effects has not been systematically evaluated. Portal-of-entry effects are caused by direct action of a chemical or its metabolites on tissues in the respiratory or gastrointestinal tract (or the skin, but that is not the focus here). Considerable conceptual similarity exists between inhalation and oral portal-of-entry exposure scenarios. In both cases exposures would occur due to agents entrained in the incoming media (e.g., inspired air or ingested materials) to the surface respiratory or gastrointestinal epithelial tissues. This scenario differs fundamentally from delivery of a chemical from circulating blood to organs throughout the body and uptake into target tissue. The relevant dose metric for systemic effects is generally the mass per tissue, e.g., mg/kg, whereas with portal-of-entry effects the most relevant dose metric would be based on mass of agent per surface area, e.g., mg/cm².

In the case of *Methods*, species-specific surface areas for regions within the respiratory tract are used in calculating a DAF that is specific to that region. An approach for considering an interspecies DAF for oral portal-of-entry considerations that would parallel the inhalation “portal-of-entry” DAF process would be appropriate. Such an approach would utilize species-specific surface areas for the affected area of the gastrointestinal tract of the laboratory animal and human and take into account other unique physiological differences. For example, rodents have a physiologically distinct forestomach region which humans lack as well as a different average gastrointestinal pH. Implementing such a *Methods*–like approach for the gastrointestinal tract will entail analysis of the available literature with regard to the requisite information and consideration of specific anatomical differences between rodents and humans (e.g., the forestomach). This issue, as well as recommendations for approaching it, is further addressed in Appendix C.

Summary of Assumptions and Limitations in $BW^{3/4}$ Scaling

From the preceding analysis the following is summarized concerning the underlying assumptions and limitations in the application of $BW^{3/4}$ scaling.

- Use of $BW^{3/4}$ scaling is most appropriate for toxicity where the measure of dose associated with the toxicity is area under the curve (AUC) for parent chemical or stable active metabolite following oral exposure.
- Some reports have indicated that BW scaling may not be appropriate to children due to disproportionate development of biochemical and physiological processes (Renwick and Lazarus, 1998) and differing allometric patterns among various sized individuals of the same species (Rhomborg and Lewandowski, 2004). However, recent work contradicts that by demonstrating that $BW^{3/4}$ relationship is descriptive of TK differences among ages including early and very early life

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

stages, down to about 2 months (Ginsberg et al., 2002 and 2004; Hattis et al., 2004).

- For oral “portal-of-entry” (POE) effects, development of a dosimetric adjustment factor involving aspects relating dose to a surface area at or within the portal is considered appropriate.
- Use of $BW^{3/4}$ scaling of orally administered for acute, lethal exposures may be less accurate than for other exposures, as some species differ from the expected norm (Hattis 2003b). It is considered more appropriate for less severe acute effects in which the functional status of physiological processes are comparable to the chronic scenario.

V. Conclusions

The recommended default procedure (in lieu of information indicating an alternate approach) for extrapolating from laboratory animal oral exposure estimates to human equivalent estimates is body weight scaling to the $3/4$ power ($BW^{3/4}$). The arithmetic involved in the application of this procedure to a given exposure scenario in representative animal species is demonstrated in Appendix B. Implementation of this scientifically based, default dosimetric adjustment, which is already employed in the derivation of oral cancer slope factors, provides a parallel to the default dosimetric approach employed in derivation of the HEC for inhalation exposures.

Pending or in lieu of the development of specific information to employ an interspecies dosimetric adjustment based on dose to the specific site of toxicity within the GI tract, the $BW^{3/4}$ -based DAF is recommended as the default to derive a HED involving oral portal-of-entry toxicity (e.g., see Appendix C). This science policy based decision provides consistency with methods used for scaling oral exposures for cancer assessment (USEPA 2005).

Default Procedure in the Hierarchy of Approaches

This default approach (as in the case of the HEC default approach) represents the bottom tier in the hierarchy of approaches to be considered in extrapolating from laboratory animal to human equivalent oral exposure scenarios for the purposes of developing a dose-response assessment pertinent to human risk assessment. A customization of the hierarchy presented in *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (USEPA 1994, see also Appendix D), for the purposes of the oral route extrapolation, is shown in the following text box.

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

Alternate Approaches

An overriding aspect of the hierarchy in Table 3 is the incorporation of mechanistic data as feasible, ensuring that the methodology employed for a particular chemical assessment is commensurate with the available data. Whichever approach is employed, the individual chemical assessment is to include text clearly describing the consideration of the available information in the selection of approaches. When the default is employed, it is to be explicitly recognized that the default has its basis in our knowledge of other chemicals.

Table 3. Hierarchy/framework of approaches for interspecies extrapolation

{optimal} If available, employ PBTK (or PBTK-TD) modeling.

{intermediate} Assess available information, considering what is known about species differences, and the toxicokinetic and toxicodynamics of the chemical. Use this information to deviate from default as appropriate (e.g., different UF or different scaling function or combination of the two), or to accept the default).¹

{default} In lieu of useful information about the chemical being considered (see intermediate approach), the default is employed.

¹ Evaluate information available for laboratory animals compared to human with respect to:

- active toxicant - parent vs active metabolite,
- appropriate dose metric (e.g. Cmax, AUC, TACC[time-above-critical concentration], age-related concentration x times interval),
- critical TD events, and
- critical effect, including consideration of portal-of-entry

Basic issues in this consideration include:

- what would be one's best quantitative judgment of the residual uncertainty in animal to human extrapolation that remains after BW scaling? ; and
 - is an alternate approach to scaling/extrapolation indicated?
-

The HED & Interspecies Uncertainty Factor, UF_A

With the implementation of this policy, the oral RfD, like the inhalation RfC, will be derived from the human equivalent exposure, an HED, for the critical effect(s) by

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

consistent application of UFs. The UFs are applied to account for various recognized uncertainties in the extrapolations from the experimental data conditions to an estimate appropriate to the assumed human scenario (see USEPA 2002). For the extrapolation from experimental animals, *Methods* currently recommends that the default value for the animal to human uncertainty factor be 3 when the default dosimetric adjustments are employed. Further *Methods* recommends that the use of more rigorous dosimetric adjustments may allow additional modification of the UF. Although *Methods* generally describes the default dosimetric adjustment as accounting for variability in disposition or toxicokinetics, *Methods* also states that the processes pertinent to the uncertainty factor include both toxicokinetics and toxicodynamics, indicating that the toxicokinetics vs toxicodynamics assignment reflects these considerations. Additional discussion on this point appears in Jarabek (1995) and Bogdanffy and Jarabek (1995).

In considering the recommendation regarding the default value for UF_A when the default $BW^{3/4}$ scaling approach is used (i.e., in lieu of information indicative of an alternate approach), various options were considered, ranging from no change in the default of 10 to 1. The conclusion to reduce the UF from its current default value of 10 is a science policy decision based on the qualitative recognition that current scientific knowledge indicates that $BW^{3/4}$ scaling generally addresses the potential for species differences in both kinetic and dynamic processes, which the UF_A has been intended to address. Additionally, it is recognized that in the situation in which defaults are invoked, uncertainties remain. Thus, when $BW^{3/4}$ scaling is applied the recommendation is that the default value for the interspecies UF_A be set at 3.

This recommended reduction of the default value from 10 to 3 is generally consistent with the approach for this uncertainty factor in *Methods* (as described in the preceding paragraph) and in EPA's cancer guidelines (USEPA 2005). As discussed in the previous sections, the scaling of chronic oral exposure via $BW^{3/4}$ addresses notable aspects of predominantly toxicokinetic and some toxicodynamic processes, yet leaving some residual uncertainty, which may flow from either area. As per *Methods*, it is recommended that with the use of more rigorous dosimetric adjustments in deriving the oral HED, there may be additional modification of the UF. That is, implementation of the recommended approach explicitly endorses a case by case evaluation with consideration of all available data in determining the reduction of the uncertainty factor (with the default of 3 applied in lieu of data indicative of an inappropriate scaling via $BW^{3/4}$). And similar to its application for the RfC, processes pertinent to the consideration of this UF are recognized to include both toxicokinetics and toxicodynamics, as including relevance of the laboratory animal model and species sensitivity. Thus, while different concepts are emphasized in the default oral vs inhalation dosimetric adjustment approaches, there are some similarities in the residual uncertainty and consequently in the recommended default value for the UF_A .

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

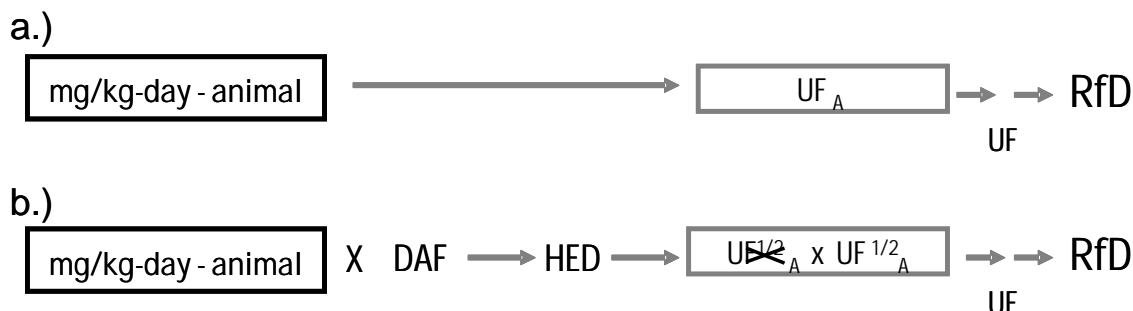


Figure 2. Procedures for (a.) the current RfD and (b.) recommended RfD processes. In the recommended process, a “human equivalent” dose or HED is derived in the case of the RfD. $BW^{3/4}$ is included here as a “Dosimetric Adjustment Factor” (DAF) or kinetic equivalence factor that is to be applied in the derivation of an HED. UF_A denotes the interspecies or animal-to-human uncertainty factor and is divided into 2 separate components without designation of either TK or TD, but equal to one half, logarithmically, of the 10^1 value typically assigned to this UF. With the application of the default, one component is dropped. In the absence of additional data informing consideration of interspecies differences, a residual default interspecies uncertainty factor of 3 remains.

Summary

Instituting procedures by which the target-tissue or some form of internal dose is estimated, in this case through calculation of a human equivalent dose or “HED”, is conceptually compatible with the overarching paradigm that regards mode-of-action as central to understanding toxicity.

Adopting $BW^{3/4}$ scaling as a means to make dosimetric adjustments in calculating a Human Equivalent Dose, an HED, brings about harmonization of RfD procedures with the RfC *Methods* wherein the inhalation parallel of the HED, the HEC, is derived.

Adopting and using $BW^{3/4}$ procedures in deriving an RfD harmonizes with its existing use in oral quantitative cancer assessment.

As with the RfC *Methods*, a hierarchy of models and procedures for interspecies extrapolation is established. $BW^{3/4}$ is acknowledged as the default approach for the oral route with more sophisticated models being considered as being more informed manners by which the internal dose may be estimated.

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

Pending or in lieu of the development of specific information to employ an interspecies dosimetric adjustment based on dose to the specific site of toxicity within the GI tract, the $BW^{3/4}$ -based DAF is recommended as the default to derive an HED involving oral portal-of-entry toxicity.

With the calculation of an HED using the default dosimetric adjustment approach, a default value of 3 is recommended for the UF_A .

Use of $BW^{3/4}$ scaling in derivation of the oral reference dose, the RfD, parallels its use as a default procedure in adjusting laboratory animal administered oral doses for derivation of human oral cancer slope values as per the most recent Cancer Guidelines. Adoption of this procedure thus provides harmonization between the two main agency dose-response assessment methodologies.

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

VI. References

Aharonson EF, Menkes H, Gurtner G, Swift DL, Proctor DF. 1974. Effect of respiratory airflow rate on removal of soluble vapors by the nose. *J Appl Physiol* 37(5):654-7.

Anderson, E.L., and the Carcinogen Assessment Group of the U.S. EPA. 1983. Quantitative Approaches in Use to Assess Cancer Risk. *Risk Anal.* 3:277-95.

Beck, BD and Clewell HJ III. 2001. Uncertainty/safety factors in health risk assessment: opportunities for improvement. *Hum Ecol Risk Assessment* 7(1): 203-207.

Bogdanffy, MS and Jarabek, AM. 1995. Understanding mechanisms of inhaled toxicants: implications for replacing default factors with chemical-specific data. *Tox Let* 82/83: 919-932.

Boxenbaum, H. 1982. Interspecies scaling, allometry, physiological time, and the ground plan of pharmacokinetics. *J Pharmacol Biopharm* 10:201-227.

Clewell HJ, Gentry PR, Covington TR, Sarangapani R, Teeguarden JG. 2004. Evaluation of the potential impact of age- and gender-specific pharmacokinetic differences on tissue dosimetry. *Toxicol Sci.* 79(2):381-93.

Clewell, HJ, Andersen, ME, and Barton, HA. 2002. A consistent approach for the application of pharmacokinetic modeling in cancer and noncancer risk assessment. *Environ. Health Perspect* 110(1): 85-93.

Dedrick RL. 1973. Animal scale-up. *J Pharmacokinet Biopharm.* 1(5):435-61.

Dedrick, RO, Bischoff, KB, and Zaharko, DS. 1970. Interspecies correlation of plasma concentration history of methotrexate (NSC-740). *Cancer Chemother Rep Pt.*, 54: 95-101.

Dourson ML, LA Knauf and JC Swartout. 1992. On reference dose (RfD) and its underlying toxicity data base. *Toxicol Industr Health* 8(3):171-189.

Enquist, BJ; Brown, JH; West, GB. 1998. Allometric scaling of plant energetics and population density. *Nature*, 395 (No. 6698):163-165.

Freireich EJ, Gehan EA, Rall DP, Schmidt LH, Skipper HE. 1966. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. *Cancer Chemother Rep.* 50(4):219-44.

Ginsberg, G, Hattis, D, Sonawane, B, Russ A, Banati P, Kozlak, M, Smolenski S, Goble R. 2002. Evaluation of Child/Adult Pharmacokinetic Differences from a Database Derived from the Therapeutic Drug Literature. *Toxicol Sci* 66: 185-200.

Ginsberg G, Hattis D, Miller R, Sonawane B. 2004. Pediatric pharmacokinetic data: implications for environmental risk assessment for children. *Pediatrics* 113(4 - Suppl):973-83.

Hanna LM, Lou SR, Su S, Jarabek AM. 2001. Mass transport analysis: inhalation RfC methods framework for interspecies dosimetric adjustment. *Inhal Toxicol.* 13(5):437-63.

Hattis, D. 2004. Role of Dosimetric Scaling and Species Extrapolation in Evaluating Risks Across Life Stages .IV. Pharmacodynamic Dosimetric Considerations. EPA/

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

Hattis, D., Goble, R., Russ, A., Chu, M, and Ericson, J. 2004. Age-related differences in susceptibility to carcinogenesis—a quantitative analysis of empirical animal bioassay data. *Environmental Health Perspectives* 112 (11): 1152-1158.

Hattis D, Ginsberg G, Sonawane, B, Smolenski S, Russ A., Kozlak M, Goble R. 2003. Differences in pharmacokinetics between children and adults- II. Children's variability in drug elimination half-lives and in some parameters needed for physiologically-based pharmacokinetic modeling. *Risk Anal* 23(1): 117-142.

Hattis D, Walker K, Russ A, Goble R. 2003b. Role of Dosimetric Scaling and Species Extrapolation in Evaluating Risks Across Life Stages. I. Dosimetric Considerations in Childhood. EPA/

Jarabek, AM. 1995a. Interspecies extrapolation based on Mechanistic Determinants of Chemical Disposition. *Hum Ecol Risk Assess*: 1(5): 641-662.

Jarabek AM. 1995b. The application of dosimetry models to identify key processes and parameters for default dose-response assessment approaches. *Toxicol Lett* 79(1-3): 171-184.

Kedderis GL. 1997. Extrapolation of in vitro enzyme induction data to humans in vivo. *Chem Biol Interact* 6;107(1-2):109-21.

Kirman, CR, Sweeney, LM, Meek, ME and Gargas, ML. 2003. Assessing the dose-dependency of allometric scaling performance using physiologically based pharmacokinetic modeling. *Reg Toxicol Pharmacol* 38:345-367.

Kleiber, M. 1932. Body size and metabolism. *Hilgardia* 6: 315-353.

Kleiber, M. 1961. *The fire of life: an introduction to animal energetics*. Wiley, New York.

Lindstedt, S.L. and Calder, W.A. 1981. Body size, physiological time, and longevity of homeothermic animals. *Quart. Rev. Biol.* 56:1-16.

Mahmood, I. 1999. Allometric issues in drug development. *J Pharm Sci* 88(11):1101-1106.

NRC (National Research Council) 1994. *Science and Judgment in Risk Assessment*. National Academy Press, New York.

O'Flaherty, EJ. 1989. Interspecies conversion of kinetically equivalent doses. *Risk Analysis* 9(4): 587-598.

Renwick, A.G. 1998. Toxicokinetics in infants and children in relation to the ADI and TDI. *Food Add. Contam.* 15, Suppl.:17-35.

Renwick AG, Lazarus NR. 1998. Human variability and noncancer risk assessment--an analysis of the default uncertainty factor. *Regul Toxicol Pharmacol.* 27(1 Pt 1):3-20.

Rhomberg, L.R. 2002. Dose scaling and extrapolation across age groups. *Human and Ecological Risk Assessment* 8(4): 783-803.

Rhomberg, L.R., and L.C. Caprario. 1999. Cross-species and cross-route comparisons of acute lethal doses: Further results of analysis of a large database. *In: Society for Risk Analysis Annual Meeting*, December 6, 1999.

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

Rhomberg, L.R. and Wolff, S.K. 1998. Empirical scaling of single oral lethal doses across mammalian species base on a large database. *Risk Anal.* 18:741-753.

Rhomberg, LR and Lewandowski, TA. 2004. Methods for identifying a default cross-species scaling factor. Submitted to USEPA Under Contract No. 3W-0477-NASX.

Schein PS, Davis RD, Carter S, Newman J, Schein DR, Rall DP. 1970 .The evaluation of anticancer drugs in dogs and monkeys for the prediction of qualitative toxicities in man. *Clin Pharmacol Ther.*11(1):3-40.

Travis, C.C., White, R.K., and Ward, R.C. 1990. Interspecies extrapolation of pharmacokinetics. *J. Theor. Biol.* 142:285-304.

Travis, C.C. 1990. Tissue dosimetry for reactive metabolites. *Risk Analysis* 10:317-321.

Travis CC and White, RK. 1988. Interspecies scaling of toxicity data. *Risk Analysis* 8(1): 119-125.

USEPA. 1980. Appendix C. Guidelines and methodology used in the preparation of health effect assessment chapters of the consent decree water quality criteria documents 45(231):79347-79357

USEPA. 1985. Health Assessment Document for Dichloromethane (methylene chloride). EPA 600/8-82/004F. Office of Health and Environmental Assessment, Washington, DC.

USEPA 1986. Guidelines for Carcinogen Risk Assessment. *Federal Register* 51 (185): 33992 – 34003.

USEPA 1987. Update to the Health Assessment Document and Addendum for Dichloromethane (Methylene Chloride): Pharmacokinetics, Mechanism of Action, and Epidemiology. External Review Draft. EPA/600/8-87/030A. Office of Health and Environmental Assessment, Washington, DC.

USEPA 1988. Recommendations for and Documentation of Biological Values for Use in Risk Assessment, EPA/600/6-87/008. Office of Research & Development, Washington, DC

USEPA 1989. Interim Methods for Development of Inhalation Reference Doses. EPA/600/8-88/066F. Office of Health and Environmental Assessment, Washington, DC.

USEPA. 1992. Draft Report: A cross-species scaling factor for carcinogen risk assessment based on equivalence of $\text{mg/kg}^{3/4}/\text{Day}$; Notice. *Federal Register* 57(109): 24152-2424173. Friday, June 5, 1992.

USEPA (U.S. Environmental Protection Agency). 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, EPA/600/8-90/066F.

USEPA (U.S. Environmental Protection Agency). 2001. Notice of Opportunity to Provide Additional Information and Comment. *Federal Register* 66 (230): 59593-59594. Thursday, November 29, 2001.

USEPA. 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. Risk Assessment Forum, Washington DC. Available at www.epa.gov/cancerguidelines.

Watanabe K, Bois FY, Zeise L. 1992. Interspecies extrapolation: a reexamination of acute toxicity data. *Risk Anal* 12(2):301-10.

West, GB; Brown, JH; Enquist, BJ. 1997. A general model for the origin of allometric scaling laws in biology. *Science*, 276 (No.5309):122-126.

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

APPENDIX A. $BW^{3/4}$ scaling vs $BW^{1/1}$ – a comparison

As currently done, the use of an interspecies uncertainty factor (UF_A) applied directly to an animal experimental dose reported in mg/kg-day is the same as scaling $BW^{1/1}$ and factoring in uncertainty. When proceeding from a small to a larger animal this procedure is not “conservative” in that it actually produces higher oral dose rates in comparison to $BW^{3/4}$ scaling procedures as shown in Table C. This analysis also demonstrates the nonproportionality of the $BW^{3/4}$ scaling processes. The smaller the animal being scaled from, the smaller the scaled human dose, about 4-fold different from $BW^{1/1}$ when scaling from rats and about 7-fold different from $BW^{1/1}$ when scaling from mice. Calculations of direct scaling (i.e., $BW^{1/1}$) and for a human are given in this table to facilitate comparison.

A common point of confusion in understanding and performing BW scaling is the expression of the experimental dose that will be scaled. In Table C below showing examples of $BW^{3/4}$ scaling, note that what is being scaled is the absolute intake or exposure, in mg not, for example, mg/kg. For example, it is the absolute exposure of 0.25 mg to the mouse that is scaled to the human by the $BW^{3/4}$ animal to human scaling factor of 385 to arrive at the absolute (and scaled) exposure of 96.25 mg. The mg/kg value is then derived by applying the human weight to this exposure, 96.25 mg/ 70 kg, to arrive at the 1.4 mg/kg scaled human intake. Scaling of mg/kg (which is actually a rate process) rather than absolute mg, may be undertaken directly but with transformations of the $BW^{3/4}$ relationship that are used to scale rate processes, e.g., $BW^{-1/4}$. This procedure is addressed in Appendix D in derivation of the DAF. The reports of Clewell et al. (2002) and O’Flaherty (1989) both contain clear examples and helpful specifics in performing BW scaling.

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

Table C. Comparison of $BW^{1/1}$ and $BW^{3/4}$ in estimating oral exposure in humans from a 10 mg/kg exposure to rats, mice, and a dog.

Scaling	Absolute animal Intake or administered Dose	Species	BW(h)/ BW(a)	BW Scaling Factor	BW Scaled Human Intake or oral Dose (mg/kg)
$BW^{3/4}$	0.25 mg / 0.025 kg	mouse	$70 / 0.025 = 2800$	$2800^{3/4} = 385$	(385×0.25) or 96 mg / 70 kg = 1.4 mg/kg
$BW^{3/4}$	2.5 mg / 0.25 kg	rat	$70 / 0.25 = 280$	$280^{3/4} = 68$	(68×2.5) or 170 mg / 70 kg = 2.4 mg/kg
$BW^{3/4}$	120 mg / 12 kg	dog	$70 / 12 = 5.8$	$5.8^{3/4} = 3.7$	(3.7×120) or 444 mg / 70 kg = 6.4 mg/kg
$BW^{1/1}$	0.25 mg / 0.025 kg	mouse	$70 / 0.025 = 2800$	$2800^{1/1} = 2800$	(2800×0.25) or 700 mg / 70 kg = 10 mg/kg
$BW^{1/1}$	2.5 mg / 0.25 kg	rat	$70 / 0.25 = 280$	$280^{1/1} = 280$	(280×2.5) or 700 mg / 70 kg = 10 mg/kg
$BW^{1/1}$	120 mg / 12 kg	dog	$70 / 12 = 5.8$	$5.8^{1/1} = 5.8$	(5.8×120) or 700 mg / 70 kg = 10 mg/kg
none	700 mg / 70 kg	human	-	-	(700×1) or 700 mg / 70 kg = 10 mg/kg

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

APPENDIX B. The Interspecies $BW^{3/4}$ Oral Dosimetric Adjustment Factor (DAF) $BW_h^{-1/4} / BW_a^{-1/4}$

The application of a DAF in determining a human equivalent exposure (an HEE) or in the specific case of an oral exposure, a human equivalent dose (an HED) would typically be applied to the laboratory animal dose (in mg/kg) as:

$$\text{Laboratory animal exposure (mg/kg)} \times \text{DAF} = \text{HED (mg/kg)}$$

This equation demonstrates the mechanics of application of the DAF to attain an HEE (HED). An analysis of DAFs, such as those derived and then applied to derive an HEC (see RfC *Methods*) reveal that they are actually composed of determinants that are intended to inform about the dose to the target tissue (the true determinant of risk). A DAF is applied to adjust to equivalency in both animals and humans the dose present at the target tissue, the internal dose. Predictably, this analysis also reveals that the DAF is a ratio constructed of human and animal values of those determinative of the internal dose. Application of this ratio will result in the human exposure that would bring about the same internal dose as the laboratory animal exposure to which it is applied. The DAF could be considered as a factor used to normalize or adjust an animal external exposure to the human external exposure that would produce an internal dose that is the same for both species.

For adjustments based on $BW^{3/4}$ scaling, the DAF would conceptually be a factor that would:

- reflect the scaling of the absolute exposure amount of the animal to the corresponding absolute exposure amount of a human
- reflect this human exposure on a mg/kg basis, and
- be constructed as a ratio of animal and human determinants of internal dose.

Table D lists examples of scaling from various laboratory animals to humans based on a 10 mg/kg exposure in various species (see also Table C). The column showing the ratio of these scaled human to animal exposures reflects the scaling and normalization of this value to a mg/kg basis, corresponding to the requisites described above for a DAF. The column in Table D labeled “ $BW_h^{-1/4} / BW_a^{-1/4}$ ” lists the body weights of the laboratory animals and a 70 kg human listed in this table to the negative one quarter power. The human to animal ratio of these scaled weights can be seen to correspond to the “Scaled Human / Animal Ratio”

Exposure expressed as a rate, such as mg/kg, rather than as an absolute amount, is an example of this relationship. In Table C the scaled human / animal ratios are actually the exposure of the animal scaled to the human ($BW^{3/4}$) divided by the human unscaled exposure ($BW^{1/1}$), the dividend being $BW^{-1/4}$. Table D demonstrates when this exposure (actually an exposure- or dose-rate) relationship is expressed as a ratio of humans to

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

laboratory animals(s) there is predictably parallel equivalence between this ratio and the $BW^{-1/4}$ scaling of human to animal ratio.

Table D. The human:animal $BW^{-1/4}$ ratio as the Dosimetric Adjustment Factor (DAF) used in deriving an HED from an oral animal exposure.

Scaling	10 mg/kg-day Exposure in	$BW^{3/4}$ Scaled Human Exposure (10 mg/kg-day for a 70 kg human)	Scaled Human / Animal Exposure Ratio	$BW_h^{-1/4} / BW_a^{-1/4} = \text{DAF}$
$BW^{3/4}$	Mouse (0.025 kg)	1.4 mg/kg	$1.4 / 10 = 0.14$	$0.34 / 2.5 = 0.14^*$
$BW^{3/4}$	Rat (0.25 kg)	2.4 mg/kg	$2.4 / 10 = 0.24$	$0.34 / 1.4 = 0.24$
$BW^{3/4}$	Dog (12 kg)	6.3 mg/kg	$6.3 / 10 = 0.63$	$0.34 / 0.54 = 0.63$

* The complete arithmetic calculation would be: human / mice = $70 \text{ kg}^{-1/4} / 0.025 \text{ kg}^{-1/4} = 0.345 / 2.51 = 0.137$ which is rounded to 0.14.

As pointed out elsewhere in this document (Section III), rate related processes scale across species in a manner related to both the direct ($BW^{1/1}$) and $BW^{3/4}$ aspects such that :

$$BW^{3/4} / BW^1 = BW^{-1/4}$$

As $BW_h^{-1/4} / BW_a^{-1/4}$ can be readily calculated and applied to any combination of body weights, it is designated as the $BW^{3/4}$ – based DAF, such that

$$\text{DAF} = (BW_h^{-1/4} / BW_a^{-1/4})$$

and

$$\text{laboratory animal exposure (mg/kg)} \times \text{DAF} = \text{HED (mg/kg)}$$

and by substituting

$$\text{laboratory animal exposure (mg/kg)} \times (BW_h^{-1/4} / BW_a^{-1/4}) = \text{HED (mg/kg)}$$

The arithmetically equivalent alternative formulation of this body weight relationship would be:

$$(BW_a^{1/4} / BW_h^{1/4})$$

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

APPENDIX C. The Oral DAF and Portal-of-entry Considerations.

“Systemic” vs “portal-of-entry” considerations in toxicity from oral administration

Table 1 in Section III above shows that interspecies allometric scaling via $BW^{3/4}$ is applicable over a wide range of functions and responses including kinetics and systemic toxicity (e.g., body weight loss). This has been demonstrated for the most part with information available from oral administration of various pharmaceuticals. Systemic toxicity can often be related to uptake and distribution of the agent throughout the body, with the effects being manifested as are overall metabolic processes, i.e. systemically.

Allometric scaling has not been extensively evaluated with toxicities such as those that occur at portal-of-entry tissues. Portal-of-entry is a descriptor used for those effects caused by direct action of an agent on barrier tissues at or proximal to the point of agent entry -- the respiratory tract for an agent being inhaled and the GI tract for an agent being ingested. Agents causing portal-of-entry effects are often highly water soluble and/or highly reactive such that concentrations achieved in these barrier tissues may be much higher than in blood.

Considerable physical and anatomic parallels exist between inhalation and oral portal-of-entry tissues. Both the respiratory tract and GI tract have a central lumen for the passage of agent (either inhaled vapors or ingested material), a metabolically active epithelial cell layer covered by saliva/mucous that lines the lumen, and submucosal tissues containing blood vessels and other elements. The transport processes determining movement of agent from the lumen, such as convection, diffusion, and metabolic clearance, as well as those determining movement at the lumen-tissue interface, are also commonalities. Conceptual similarity exists between inhalation and oral portal-of-entry exposure scenarios. In both cases exposures would occur due to agents entrained in the incoming media (e.g., inspired air or ingested materials) to the surface of epithelial tissues, either respiratory or gastrointestinal.

In portal-of-entry exposure scenarios, agent is typically delivered directly to the surface of target tissue. This differs fundamentally from systemic exposure scenarios where delivery of an agent is from circulating blood to organs throughout the body and uptake into target tissue. This difference is reflected in the relevant dose metric for these scenarios. For systemic effects, the most appropriate measure of dose (or dose metric) generally would be based on the mass of agent per tissue over the relevant period of time, e.g., body weight/day or mg/tissue mass, whereas with portal-of-entry effects the most appropriate dose metric would be based on mass of agent per surface area, e.g., mg/cm^2 .

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

Portal-of-entry considerations in the inhalation RfC Methods – application to the oral exposures

In the case of the respiratory tract, *RfC Methods* provides a hierarchy for performing respiratory tract (portal-of-entry) dosimetry with the basic default process proscribing use of species-specific physiological and anatomical measures. The default dosimetry is based on specifically where effects occur within these portal tissues. The paradigm of dose to the target-tissue being related to risk of toxicity underlies these considerations. Further, the Agency's inhalation *RfC Methods* specifies different dosimetric approaches for agents manifesting portal-of-entry *vice* systemic effects giving over considerable discussion as to why different approaches are advised. Application of these procedures are directed at deriving a dosimetric adjustment factor, a DAF, in calculating a human equivalent exposure (HEE) or concentration (HEC) for these portal-of-entry effects.

In the case of the GI tract such specific considerations are yet to be formally developed for dosimetry regarding oral portal-of-entry effects. Nevertheless, because of the conceptual similarities in exposure between these portal-of-entry tissues, some approaches may be hypothesized for application for the oral scenario from the procedures within the inhalation *RfC Methods*.

Rationale for an “oral portal-of-entry” DAF

In *Methods* the basic default “portal-of-entry” scenario for inhalation dosimetry involves use of species-specific physiological and anatomical measures such as ventilation volumes and rates and surface areas of various regions within the respiratory tract. A parallel approach to the *Methods* process could be considered appropriate for considering an interspecies DAF for oral portal-of-entry. The basic relationship of measures specified in the default inhalation scenario is minute ventilatory volume (V_E) divided by the surface area of a specified region of the respiratory tract (SA_{RT}). Using the ventilatory volume as a surrogate for mass of agent inhaled, this relationship would result in units of “mass per surface area” as discussed above. The parallel oral construction would be considered, for example, to be ingestion rate (Q) divided by the surface area of a specified region of the GI tract (SA_{GI}), such that:

$$V_E / SA_{RT} \parallel Q / SA_{GI}$$

In this case the ingestion rate is the surrogate for mass of agent ingested. This relationship would similarly result in “mass per surface area”.

Implementation of such a conceptually sound approach as shown in the equation above (or any other proposed approach) requires interpretive analysis of existing information or possibly generation of other specific empirical information. These analyses and data could, for example, address such areas as interspecies anatomical differences (such as the lack of a human anatomical parallel to the rodent forestomach),

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

surface areas of the GI tract in both laboratory animals and humans, rates and scenarios of ingestion, or diffusion rates, uptake rates, etc. Integration of this empirical information into appropriate models, for example those estimating clearance or fractional penetration (*as per* Aharonson et al., 1974 or Hanna et al., 2001) or a valid physiologically-based toxicokinetic (PBTK) model parameterized for both animal and humans, would also facilitate implementation.

Another approach for oral portal-of-entry dosimetry that may be hypothesized would be to explore the allometric interrelationships of the various measures that define the dose to target tissue relationship as per the equation above. For example, Appendix D describes the derivation of and gives rationale and specifics in developing what may be considered an oral systemic DAF based on BW scaling relationships. That recommendation involves constructing an interspecies ratio of $BW^{3/4}$ scaled body weights normalized against body weight scaled directly, i.e., $BW^{1/1}$, to give an estimate of an interspecies DAF. The rationale for this derivation is that rate related processes scale across species in a manner related to both the direct ($BW^{1/1}$) and $BW^{3/4}$ aspects in accordance with the relationship of $BW^{3/4} / BW^1 = BW^{-1/4}$. Similarly, the oral measures proposed in the equation presented in this Appendix have allometries that may also be related to BW. The oral measure of Q has been shown to exhibit an interspecies relationship related to $BW^{3/4}$ (Table 1). Interspecies body surface area has been demonstrated to scale in the relationship of $BW^{2/3}$. Theoretically, an equation parallel to this equation could be constructed using these allometries. As indicated above, such an approach would require a systematic analysis of appropriate information as per *Methods* to establish scaling relationships between species of various internal tissue surface areas.

Recommendations regarding DAF and “portal-of-entry” effects

The conceptual similarities between the inhalation and oral portals-of-entry makes development of an oral portal-of-entry DAF feasible. In cases where the specific information needed is not available, however, a pragmatic default approach is needed.

Before proposing a pragmatic default approach two points should be noted concerning the default “systemic” DAF approach and existing Agency procedures. First, an analysis of the default systemic DAF (Table C) shows that the actual magnitude of the correction factor applied to the laboratory animal exposure varies (depending on strain) from about four for rats ($1/0.24 = 4.1$) and about 7 for mice ($1/0.14 = 7.1$). In combination with the default residual portion of the UF_A (a value of 3) the cumulative factor applied using $BW^{3/4}$ in a default scenario (i.e., where available information does not indicate an alternative approach or include data pertaining to species differences) could range from about 12-fold for rats and 21-fold for mice. These values in that default scenario would lower the laboratory animal exposures more than the preexisting default UF_A factor of 10 and are therefore more risk adverse. Second, existing cancer procedures for calculation of oral slope factors do not recognize or make accommodations for portal-of-entry effects (tumors), but rely solely on $BW^{3/4}$ for HEE development.

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

Based on this analysis, se of $BW^{3/4}$ (specifically $BW_h^{-1/4}/BW_a^{-1/4}$; see Appendix D) is proposed as a pragmatic and reasonable approach to use in development of a default DAF for oral portal-of-entry effects in cases lacking the appropriate animal and human information needed to develop a chemical specific DAF. That DAF would, as with the parallel inhalation DAF, be based on the concept of dose to a target surface area. When such requisite information is available for a chemical via the oral route, then an approach analogous to that used for inhalation could be used to develop a proposed default oral “portal-of-entry” DAF for purposes of comparison against other alternative approaches.

DISCLAIMER: THIS INFORMATION IS DISTRIBUTED SOLELY FOR THE PURPOSE OF EXTERNAL REVIEW UNDER APPLICABLE INFORMATION QUALITY GUIDELINES. IT HAS NOT BEEN FORMALLY DISSEMINATED BY THE EPA AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

APPENDIX D. Hierarchy of approaches for interspecies extrapolation for inhalation dosimetry (from USEPA 1994)

Optimal Approach (e.g., PBTK modeling)

- Based on sufficient data to support a model structure that will describe all significant mechanistic determinants of chemical disposition, toxicant-target interaction, and tissue response
- Uses chemical-specific and species-specific parameters
- Dose metric described at level of detail commensurate to response data

Immediate Approaches

Default Approach

- Based on general (non-chemical specific) understanding of mechanistic determinants of chemical disposition, toxicant-target interaction, and tissue response
 - May use categorical or default values for chemical and species parameters
 - Dose metric described at generic level commensurate to response data
-

Adapted (slightly) from Table 3-6 of USEPA. 1994. *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*. EPA/600/8-90/066F, NCEA, RTP, North Carolina.